Negative Regulation of the SH2-homology-containing Protein-tyrosine Phosphatase-1 (Shp-1) P2 Promoter by the HTLV-1 Tax Oncoprotein

Retrovirology

Poster presentation

Negative regulation of the SH2-homology-containing protein-tyrosine phosphatase-1 (Shp-1) P2 promoter by the HTLV-1 tax oncoprotein

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Expression of SH2-Homology-Containing Protein-Tyrosine Phosphatase-1 (Shp-1), a candidate tumor suppressor, is repressed in HTLV-1 transformed lymphocyte cell lines, leukemic cells of Adult T-cell Leukemia (ATL) patients and other hematologic malignancies. However, the mechanisms underlying regulation and repression of Shp-1 remain unclear. Herein, we cloned the putative full-length, hematopoietic cell specific Shp-1 P2 promoter and identified a 277 bp "core" promoter region. In a dose-dependent manner, wild type HTLV-1 Tax and its M22/M47 mutant derivatives profoundly inhibited Shp-1 P2 promoter activity. NF-kB, not CBP or p300, was found to markedly stimulate basal P2 promoter activity and reverse Tax-induced Promoter Silencing (TIPS) in Jurkat cells. Mutagenesis of two NF-kB binding sites in the core promoter region led to only modest inhibition of basal promoter activity but to complete loss of TIPS. Further studies show that TIPS is potentiated by the histone deacetylase-1 (HDAC1) and in co-immunoprecipitation studies NF-kB could compete with HDAC1 for association with Tax protein. In addition, chromatin immunoprecipitation (ChIP) studies showed that Tax recruits HDAC1 to the core promoter and displaces NF-kB binding. We propose that in TIPS, Tax recruits HDAC1 to the Shp-1 P2 promoter which results in deacetylation and dissociation of NF-kB from the promoter leading to attenuation of Shp-1 expression, thus providing a possible first step toward leukemogenesis through its silencing of this key immediate early negative regulator of IL-2 signaling.